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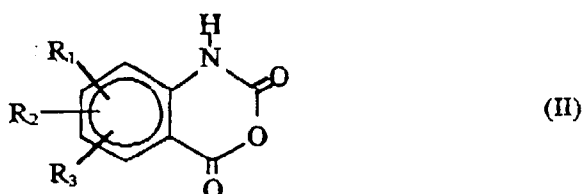
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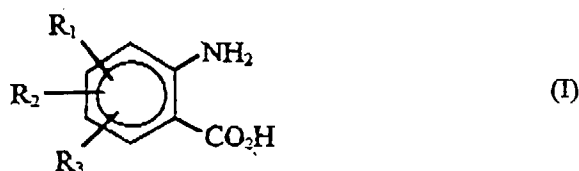
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London WC1R 5LX (GB)(54) **Process for producing isatoic anhydrides**

(57) A process for producing isatoic anhydrides of the formula (II):



which comprises reacting an anthranilic acid of formula (I):



or a salt thereof with phosgene

using a mixed solvent of water and an organic solvent miscible with water and inert to the reaction;

conducting the reaction in the presence of an alkylpyridinium salt in an aqueous solvent; or

using a mixed solvent of water and a specific amount of an organic solvent substantially immiscible with water and inert to the reaction.

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Description

The present invention relates to a process for producing isatoic anhydrides. More particularly, it relates to a process for producing isatoic anhydrides using corresponding anthranilic acid or a salt thereof and phosgene.

Isatoic anhydrides are useful as an intermediate of an antiphlogistic, a remedy for diabetic complication, etc as described, in JP-A-62-97476. As the production process, for example, there is known that isatoic anhydrides are produced by using corresponding anthranilic acid or a salt thereof and phosgene in the presence of a water solvent (J. Org. Chem., 26, 613 (1961)).

However, the above process using water as the solvent had an industrial problem that the reaction mixture changes into a whipped cream state and, therefore, a volume efficiency of a reactor is very low and a yield of the objective product is not satisfactory.

The present inventors have intensively studied about the process for producing isatoic anhydrides so as to solve these drawbacks.

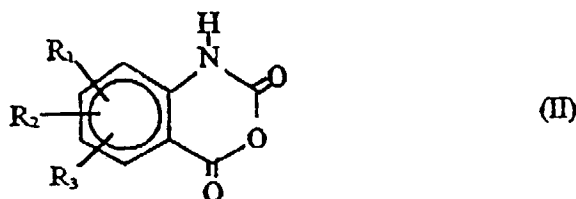
As a result, it has been found that, by using a mixed solvent consisting of water and an organic solvent which is miscible with water and is inert to the reaction, in place of water conventionally used as the reaction solvent, it becomes possible to inhibit the formation of whipped cream mass from the reaction mixture, thereby remarkably improving not only the volume efficiency of the reactor but also the yield.

The present inventors have also found, by using a specific compound, an alkylpyridinium salt, in the reaction, inhibition of the formation of whipped cream mass from the reaction mixture, that is, the remarkable improvement of volume efficiency of the reactor as well as of the yield, can be attained.

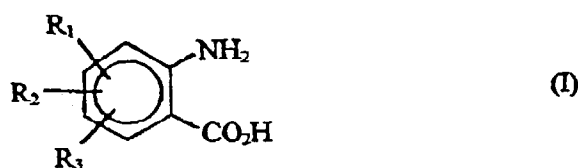
The present inventors have further found that, by using a mixed solvent consisting of water and a specific amount of an organic solvent which is substantially immiscible with water and is inert to the reaction in place of water conventionally used as the reaction solvent, it is also possible to solve the above-mentioned problems of the conventional method.

Thus, the present invention has been accomplished.

That is, the present invention provides a process for producing isatoic anhydrides represented by the formula (II) :



wherein R_1 and R_2 , which may be the same or different, each represent a hydrogen atom, a halogen atom, a nitro group, a lower alkyl group which is optionally substituted with a halogen atom, an aralkyl group which is optionally substituted with a halogen atom, an alkoxy group which is optionally substituted with a halogen atom, an alkoxycarbonyl group which is optionally substituted with a halogen atom, an acyloxy group or XNR_4R_5 (X is a direct bond, a lower alkylene group or a carbonyl group or carbonyloxy group in which the nitrogen atom is attached to carbonyl provided that, when X is a direct bond or a lower alkylene group, R_4 and R_5 , which may be the same or different, each represent a lower alkyl group or N, R_4 and R_5 may form a five- or six-membered heterocycle which optionally contains another hetero atom and, when X is a carbonyl group, R_4 and R_5 which may be the same or different, each represent a hydrogen atom or a lower alkyl group or N, R_4 and R_5 may form a five- or six-membered heterocycle which optionally contains another hetero atom and further, when containing another hetero atom, said hetero atom may be substituted); and R_3 is a hydrogen atom, a halogen atom, a nitro group, a lower alkyl group which is optionally substituted with a halogen atom, an aralkyl group which is optionally substituted with a halogen atom, an alkoxy group which is optionally substituted with a halogen atom or an alkoxycarbonyl group which is optionally substituted with a halogen atom, which comprises reacting phosgene and an anthranilic acid represented by the formula (I):



wherein R_1 , R_2 and R_3 are as defined above, or a salt thereof using a mixed solvent comprising water and an organic solvent which is miscible with; water and inert to the reaction.

In this specification, including the accompanying claims, unless otherwise specified: alkyl groups and moieties may be straight- or branched-chain and generally contain from 1 to 6 carbon atoms; alkylene groups may be straight- or branched-chain and generally contain from 1 to 6 carbon atoms; and hetero atoms are generally chosen from O, S and N.

The present invention also provides a process for producing an isatoic anhydride compound of the formula (II) which comprises reacting phosgene and an anthranilic acid compound of the formula (I) or a salt thereof in the presence of an alkylpyridinium salt.

The present invention further provides a process for producing an isatoic anhydride compound of the formula (II) which comprises reacting phosgene and an anthranilic acid compound of the formula (I) or a salt thereof using a mixed solvent comprising water and an organic solvent which is substantially immiscible with water and inert to the reaction, the amount of the organic solvent being in a range of 1.5 - 20 fold by weight or more with respect to the amount of an anthranilic acid compound of the formula (I) or a salt thereof.

Hereinafter, the present invention will be described in detail.

The substituents R_1 and R_2 in anthranilic acids (I) as the raw material of the present invention independently indicate a hydrogen atom, a halogen atom, a nitro group, a lower alkyl group which is optionally substituted with a halogen atom, an aralkyl group which is optionally substituted with a halogen atom, an alkoxy group which is optionally substituted with a halogen atom, an alkoxycarbonyl group which is optionally substituted with a halogen atom, an acyloxy group or XNR_4R_5 (X is a direct bond, a lower alkylene group or a carbonyl group provided that, when X is a direct bond or a lower alkylene group, R_4 and R_5 independently indicate a lower alkyl group or N, R_4 and R_5 may form a five- or six-membered heterocycle which optionally contains another hetero atom and, when X is a carbonyl group, R_4 and R_5 independently indicate a hydrogen atom or a lower alkyl group or N, R_4 and R_5 may form a five- or six-membered heterocycle which optionally contains another hetero atom and further, when containing another hetero atom, said hetero atom can be substituted); and R_3 is a hydrogen atom, a halogen atom, a nitro group, a lower alkyl group which is optionally substituted with a halogen atom, an aralkyl group which is optionally substituted with a halogen atom, an alkoxy group which is optionally substituted with a halogen atom or an alkoxycarbonyl group which is optionally substituted with a halogen atom.

Examples of the halogen atom include chlorine, bromine and fluorine.

Examples of the lower alkyl group which is optionally substituted with the halogen atom include lower alkyl group such as methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, i-pentyl and hexyl; monohalo lower alkyl group such as chloromethyl, bromomethyl and chloropropyl; dihalo lower alkyl group such as 1,2-dichloroethyl, 1,2-dibromoethyl and, 2,2-dichloroethyl; and trihalo lower alkyl group such as trifluoromethyl.

Examples of the aralkyl group which is optionally substituted with the halogen atom include benzyl, phenylethyl, 4-chlorobenzyl, 2,4-dichlorobenzyl and 2,4-dibromobenzyl.

Examples of the alkoxy group which is optionally substituted with the halogen atom include lower alkoxy group such as methoxy, ethoxy, propoxy, i-propoxy, butoxy, i-butoxy, t-butoxy, pentyloxy, i-pentyloxy, hexyloxy, etc.; and lower alkoxy group substituted with the halogen atom, such as chloromethoxy, bromomethoxy, 1-, 2-chloroethoxy, 1-, 2-, 3-chloropropoxy, dichloromethoxy, dibromomethoxy, 1,2-dichloroethoxy, 2,2-dichloroethoxy and trifluoromethoxy.

Examples of the alkoxycarbonyl group which is optionally substituted with the halogen atom include the same carbonyl group having the alkoxy group which is optionally substituted with the halogen atom as described above.

Examples of the acyloxy group include lower alkylcarbonyloxy group such as acetoxyl, propionyl, butyryl, i-butyryl, valeryl, i-valeryl and pivaloyl, and arylcarbonyloxy group such as benzoyl.

Examples of the lower alkylene group in XNR_4R_5 include methylene, dimethylene, trimethylene and tetramethylene. Examples of R_4 and R_5 as the lower alkyl group in NR_4R_5 include the same lower alkyl group as described above. Specific examples thereof include dimethylamino, diethylamino, dipropylamino and dibutylamino.

Specific examples of a five- or six-membered heterocycle formed by N, R_4 and R_5 in case that N, R_4 and R_5 in NR_4R_5 form a heterocycle which optionally has another hetero atom are pyrrol, 2H,4H-pyrrolyl, pyrrolidino, pyrazolyl, piperidino, morpholino and imidazolyl.

When another hetero atom is N, N can have a substituent. Examples of the substituent include a lower alkyl group which is optionally substituted with halogen as described above, an aralkyl group which is optionally substituted with halogen as described above, aralkyl group substituted with lower alkoxy, a phenylcarbonyl group which is optionally substituted with a lower alkoxy group, and a phenylcarbonylalkyl group (e.g. 3-phenylcarbonylpropyl).

Typical examples of the anthranilic acids (I) include anthranilic acid, 3-, 4-, 5-, 6-chloroanthranilic acid, 3-, 4-, 5-, 6-bromoanthranilic acid, 3-, 4-, 5-, 6-fluoroanthranilic acid, 3,4-, 3,5-, 3,6-, 4,5-, 5,6-dichloroanthranilic acid, 3,4-, 3,5-, 3,6-, 4,5-, 5,6-dibromoanthranilic acid, 3,4-, 3,5-, 3,6-, 4,5-, 5,6-difluoroanthranilic acid, 3-bromo-4-chloroanthranilic acid, 3-bromo-5-chloroanthranilic acid, 3-bromo-6-chloroanthranilic acid, 4-bromo-3-chloroanthranilic acid, 4-bromo-5-chloroanthranilic acid, 4-bromo-6-chloroanthranilic acid, 5-bromo-3-chloroanthranilic acid, 5-bromo-4-chloroan-

thranilic acid, 5-bromo-6-chloroanthranilic acid, 6-bromo-3-chloroanthranilic acid, 6-bromo-4-chloroanthranilic acid, 6-bromo-5-chloroanthranilic acid, 3-chloro-4-fluoroanthranilic acid, 3-bromo-4-fluoroanthranilic acid, 3,4,5-, 3,4,6-, 3,5,6-, 4,5,6-trichloroanthranilic acid, 3,4,5-,3,4,6-,3,5,6-,4,5,6-tribromoanthranilic acid,3,4,5-, 3,4,6-, 3,5,6-, 4,5,6-tri-fluoroanthranilic acid, 3-, 4-, 5-, 6-nitroanthranilic acid, 3-, 4-, 5-, 6-methylanthranilic acid, 3-, 4-, 5-, 6-ethylanthranilic acid, 3-, 4-, 5-, 6-propylanthranilic acid, 3-, 4-, 5-, 6-i-propylanthranilic acid, 3-, 4-, 5-, 6-methoxycarbonylanthranilic acid, 3-, 4-, 5-, 6-ethoxycarbonylanthranilic acid, 3-, 4-, 5-, 6-propoxycarbonylanthranilic acid, 3-, 4-, 5-, 6-i-propoxy-carbonylanthranilic acid, 3-, 4-, 5-, 6-t-butoxycarbonylanthranilic acid, 3-, 4-, 5-, 6-(chloromethoxy)anthranilic acid, 3-, 4-, 5-, 6-(bromomethoxy)anthranilic acid, 3-, 4-, 5-, 6-(1-chloroethoxy) anthranilic acid, 3-, 4-, 5-, 6-(2-chloroethoxy)anthranilic acid, 3-, 4-, 5-, 6-(1-chloropropoxy)anthranilic acid, 3-, 4-, 5-, 6-(2-chloropropoxy)anthranilic acid, 3-, 4-, 5-, 6-(3-chloropropoxy)anthranilic acid, 3-, 4-, 5-, 6-(dichloromethoxy)an-
 thranilic acid, 3-, 4-, 5-, 6-(dibromomethoxy)anthranilic acid, 3-, 4-, 5-, 6-(trifluoromethoxy)anthranilic acid, 3-, 4-, 5-, 6-(chloromethoxycarbonyl)anthranilic acid, 3-, 4-, 5-, 6-(bromomethoxycarbonyl)anthranilic acid, 3-, 4-, 5-, 6-(1-chlo-
 roethoxycarbonyl)anthranilic acid, 3-, 4-, 5-, 6-(2-chloroethoxycarbonyl)anthranilic acid, 3-, 4-, 5-, 6-(1-chloropropox-
 ycarbonyl)anthranilic acid, 3-, 4-, 5-, 6-(dichloromethoxycarbonyl)anthranilic acid, 3-, 4-, 5-, 6-(dibromomethoxycarb-
 onyl)anthranilic acid, 3-, 4-, 5-, 6-(1,2-dichloromethoxycarbonyl)anthranilic acid, 3-, 4-, 5-, 6-(2,2-dichloromethoxy-
 carbonyl)anthranilic acid, 3-, 4-, 5-, 6-(trifluoromethoxycarbonyl)anthranilic acid, 3-, 4-, 5-, 6-chloromethylanthranilic
 acid, 3-, 4-, 5-, 6-bromomethylanthranilic acid, 3-, 4-, 5-, 6-(1-chloroethyl)anthranilic acid, 3-, 4-, 5-, 6-(2-chloroethyl)
 anthranilic acid, 3-, 4-, 5-, 6-(dichloromethyl)anthranilic acid, 3-, 4-, 5-, 6-(1,2-chloroethyl)anthranilic acid, 3-, 4-, 5-, 6-
 (2,2-dichloroethyl)anthranilic acid, 3,4-dimethylanthranilic acid, 3,4-diethylanthranilic acid, 3-benzylanthranilic acid, 3-(2-phenylethyl)anthranilic acid, 3-
 (4-chlorobenzyl)anthranilic acid, 3-(2,4-dichlorobenzyl) anthranilic acid, 3-(2,4-dibromobenzyl)anthranilic acid, 3-meth-
 oxyanthranilic acid, 3-ethoxyanthranilic acid, 3-propoxyanthranilic acid, 3-i-propoxyanthranilic acid, 4,5-dimethoxyan-
 thranilic acid, 5,6-dimethoxyanthranilic acid,3,5-diethoxyanthranilic acid, 3,6-dipropoxyanthranilic acid, 3-(N,N-dimeth-
 yl-amino)anthranilic acid, 3-(N,N-diethylamino)anthranilic acid, 3-(N,N-dipropylamino)anthranilic acid, 3-(N,N-dib-
 utylamino)anthranilic acid, 3-(1-pyrrolyl) anthranilic acid, 3-(1-imidazolyl)anthranilic acid, 3-(1-pyrazolyl)anthranilic ac-
 id, 3-(2H,4H-pyrrolyl)anthranilic acid, 3-(piperidino)anthranilic acid, 3-(morpholino) anthranilic acid, 3-(4-methylpipe-
 ridino)anthranilic acid, 3-(4-(chloromethyl)piperidino)anthranilic acid, 3-(4-benzylpiperidino) anthranilic acid, 3-(4-
 (3-methoxybenzyl)piperidino)anthranilic acid, 3-(4-(phenylcarbonylpiperidino)anthranilic acid, 5-(4-(3,4-dimethoxy-
 phenylcarbonyl)piperidino)anthranilic acid, 3-(1-pyrrolylmethyl) anthranilic acid, 3-(morpholinomethyl)anthranilic acid, 4-((4-methylpiperidino)methyl)anthranilic acid, 5- (4-(3-phenylcarbonylpropyl)
 piperidinocarbonyl)anthranilic acid, 4,6-dimethyl-5-ethyloxycarbonylanthranilic acid, 3-carbamoylanthranilic acid, 3-(N-
 methylcarbamoyl) anthranilic acid, 3-(N,N-dimethylcarbamoyl)anthranilic acid, 4-(4-methylpiperidinocarboxy) an-
 thranilic acid, 5-(4-benzylpiperidinocarboxy) anthranilic acid, 5-(4-(3-phenylcarbonylpropyl) piperidinocarboxy) an-
 thranilic acid, 4,6-dimethyl-5-ethyloxycarbonylanthranilic acid, 3-chloro-5,6-dimethoxyanthranilic acid, 4-acetoxyan-
 thranilic acid, 4-propionyloxyanthranilic acid, 4-butyryloxyanthranilic acid, 4-i-butyryloxyanthranilic acid, 4-valeryloxy-
 anthranilic acid, 4-i-valeryloxyanthranilic acid, 4-pivaloyloxyanthranilic acid and 4-benzoyloxyanthranilic acid.

The anthranilic acids (I) can also be used in the form of a salt. Either the amino group or the carboxyl group may form a salt. Examples of the salt include hydrochloride salt, sodium salt and potassium salt.

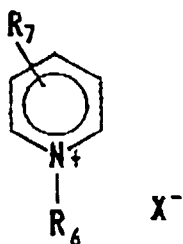
The object of the present invention can be attained by using a mixed solvent consisting of water and an organic solvent which is miscible with water and is inert to the reaction in place of water as the reaction solvent. (Hereinafter this method is referred to as Method 1.) Examples of the organic solvent which is miscible with water and is inert to the reaction include cyclic ethers such as tetrahydrofuran, dioxane; and glymes such as ethylene glycol dimethyl ether and diethylene glycol dimethyl ether. Among them, cyclic ethers, particularly tetrahydrofuran, are preferred.

The proportion of the organic solvent in the mixed solvent varies depending on the kind of anthranilic acid, the raw material, and kind of isatoic anhydride, the product, but is normally from 1 to 99% by weight, preferably from 5 to 95% by weight, more preferably from 10 to 90% by weight, further more preferably from 10 to 50% by weight, based on the total amount of the mixed solvent.

When the proportion of the organic solvent is less than 1% by weight, the effect of inhibiting the formation of whipped cream mass from the reaction mixture is liable to be lowered. Therefore, normally, not less than 1% by weight of the mixed solvent is used.

An amount of the mixed solvent used is normally from 1-to 20-fold amount by weight, preferably from 2- to 10-fold amount by weight, with respect to the amount of anthranilic acids.

The object of the present invention can also be attained by reacting the anthranilic acid compound of the formula (I) or a salt thereof with phosgene in the presence of an alkylpyridinium salt in an aqueous solvent. (Hereinafter this method is referred to as Method 2.) Examples of the alkylpyridinium salt include compounds represented by the fol-
 lowing formula (III):



(III)

wherein R_6 indicates an alkyl group having 8 - 20 carbon atoms ; R_7 indicates a hydrogen atom or a lower alkyl group and X indicates an anion.

Examples of the alkyl group having 8 - 20 carbon atoms as R_6 include n-octyl, 2-ethylhexyl, nonyl decyl, -i-decyl, undecyl, lauryl, tridecyl, myristyl, palmityl, stearyl and eicosyl. Examples of the lower alkyl group as R_7 include methyl, ethyl, propyl, i-propyl, butyl and pentyl.

X includes, for example, halogen anions such as chloride and bromide, sulfonyloxy anions such as methanesulfonyloxy, benzenesulfonyloxy and p-toluenesulfonyloxy.

Typical examples of the alkylpyridinium salt include laurylpyridinium chloride, laurylpyridinium bromide, cetylpyridinium chloride, cetylpyridinium bromide, myristyl- γ -picoliniumchloride and lauryl- γ -picolinium benzenesulfonate.

The alkylpyridinium salt is used usually in about 0.005 - 0.5 fold amount by weight, preferably about 0.01 - 0.2 fold amount by weight, more preferably about 0.05 - 0.2 fold amount by weight, with respect to the amount of anthranilic acid compound of the formula (I).

In method 2, water, the reaction solvent, is used usually in about 1 - 20 fold amount by weight, preferably about 2 - 10 fold amount by weight, with respect to the amount of anthranilic acid compound of formula (I).

Further, in Method 2, an organic solvent substantially immiscible with water and inert to the reaction may be co-used as the solvent.

Examples of the organic solvent include aromatic hydrocarbons such as benzene, toluene and xylene; halogenated hydrocarbons such as chlorobenzene, o-dichlorobenzene, m-dichlorobenzene, bromobenzene, dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; and ethers such as ethylether and di-i-propylether. Among them, aromatic hydrocarbons, halogenated hydrocarbons and the like, particularly toluene, chlorobenzene and the like, are preferred.

In method 2, the amount of the organic solvent, when used, is usually about 0.01 - 1 fold by weight, preferably about 0.1 - 0.5 fold by weight, with respect to the amount of water.

The object of the present invention can also be attained by using a mixed solvent consisting of water and an organic solvent which is substantially immiscible with water and is inert to the reaction in place of water as the reaction solvent. (Hereinafter this method is referred to as Method 3.) The amount of the organic solvent is in a range of 1.5 - 20 fold by weight, preferably 2.0 - 10 fold by weight, with respect to the amount of an anthranilic acid compound of the formula (I) or a salt thereof.

Examples of the organic solvent include aromatic hydrocarbons such as benzene, toluene and xylene; halogenated hydrocarbons such as chlorobenzene, o-dichlorobenzene, m-dichlorobenzene, bromobenzene, dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; and ethers such as ethylether and di-i-propylether. Among them, aromatic hydrocarbons, halogenated hydrocarbons and the like, particularly toluene, chlorobenzene and the like, are preferred.

In Method 1, Method 2 and Method 3, the anthranilic acids or a salt thereof is dissolved or dispersed in the reaction solvent and, thereafter, is reacted with phosgene. The reaction is normally carried out by introducing phosgene into a reactor while adjusting the pH of the reaction mixture to about 2 to 10, preferably from about 3 to 9, more preferably about 6 to 7. The reaction temperature is normally from 0 to 40°C, preferably from 0 to 20°C.

For adjusting the pH, an alkali is normally used. Examples of the alkali include alkali metal hydroxide such as sodium hydroxide and potassium hydroxide; alkaline earth metal hydroxide such as magnesium hydroxide, calcium hydroxide and barium hydroxide; alkali metal carbonate such as sodium carbonate and potassium carbonate; alkaline earth metal carbonate such as magnesium carbonate, calcium carbonate and barium carbonate; alkali metal hydrogencarbonate such as sodium hydrogencarbonate and potassium hydrogencarbonate; and alkaline earth metal oxide such as calcium oxide and barium oxide. Among them, sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate and calcium hydrogencarbonate are preferably used.

The alkalis can be used singly or as a mixture of two or more thereof. The alkali can be used after mixing with water.

In Method 1, Method 2 and Method 3, phosgene may be introduced in a vapor state or introduced in a liquid state under pressure. It is also possible to introduce phosgene dissolved in the organic solvent.

An introducing inlet of phosgene may be at the vapor phase part or liquid phase part of the reactor. When the introducing inlet is at the liquid phase, isatoic anhydrides are sometimes deposited to close the introducing inlet. Therefore, the reaction must be carried out taking this point into consideration.

An amount of phosgene introduced is normally from about 0.9-to 2 -fold molar amount, preferably from about 1-to 1.7-fold molar amount, with respect to the anthranilic acids.

It is preferred that, firstly, a predetermined amount of phosgene was introduced while maintaining the pH of the reaction mixture at 2 to 10, and, then, remaining phosgene or a mineral acid such as hydrochloric acid is added thereto until the pH becomes 2 or lower, preferably 1 or lower, thereby making it possible to improve the yield of the objective product.

Thus, the objective isatoic anhydrides are produced. When isatoic anhydrides are removed from the reaction mixture, phosgene remained is normally exhausted in the first place. Examples of such a exhaustion process include a process of purging an inert gas such as nitrogen, a process of distilling off with a solvent, and a process of adding an alcohol such as methanol to react with phosgene. It is possible to obtain isatoic anhydrides by distilling off the organic solvent from the reaction mixture after exhaustion of phosgene, followed by subjecting to separating means such as filtration.

The isatoic anhydrides thus obtained can also be further purified, if necessary.

According to the present invention, Method 1, Method 2 and Method 3, it becomes possible to inhibit the formation of whipped cream mass from the reaction mixture and the volume efficiency of the reactor is improved, thereby remarkably improving the productivity. It becomes also possible to improve yield of isatoic anhydrides, the objective product.

The following Examples further illustrate the present invention in detail but are not to be construed to limit the scope thereof.

Example 1

To a 200 ml flask equipped with a condenser (-20°C) , water (43.5 g) , tetrahydrofuran (43.5 g) and 4-chloroanthranilic acid (4.38 g, purity: 98%) were charged. After cooling to 10°C with stirring, sodium carbonate was added thereto so that the pH became 6 to 7. Then, the reaction was conducted while introducing phosgene in the vapor phase part of a reactor with a flow rate of 0.2 g/minute, cooling the reaction mixture so that the temperature was maintained at 20 to 25 °C, and adding an aqueous 10% sodium carbonate so that the pH was maintained at 6 to 7.

After 3 g of phosgene has been introduced, the addition of the aqueous sodium carbonate was stopped and phosgene was further introduced continuously until the pH became 1. The maximum value of the volume of the reaction mixture was 180 ml.

After the completion of the reaction, the reaction mixture was heated to 65°C and, after distilling off phosgene together with a part of the solvent, the resultant crystal was filtered, washed with methanol and then dried to obtain 4.4 g of 7-chloroisatoic anhydride (purity: 99%) . The yield was 88%.

The volume efficiency (yield of the objective product per maximum volume 100 ml of the reaction mixture) was 2.4 g/100 ml.

Example 2

To a 2 liter flask equipped with a condenser (-20°C) , water (510 g), tetrahydrofuran (51 g) and 4-chloroanthranilic acid (106 g, purity: 98%) were charged. After cooling to 10°C with stirring, an aqueous 23% sodium hydroxide was added thereto so that the pH became 6 to 7, Then, the reaction was conducted while introducing phosgene in a vapor phase part of a reactor with a flow rate of 0.5 g/minute, cooling the reaction mixture so that the temperature was maintained at 5 to 15 °C and adding an aqueous 23% sodium hydroxide so that the pH was maintained at 6 to 7.

After 67 g of phosgene has been introduced, the addition of the aqueous sodium hydroxide was stopped and phosgene was further introduced continuously until the pH became 1. The maximum value of the volume of the reaction mixture was 1100 ml .

According to the same manner as in Example 1, the reaction mixture was post-treated to obtain 116 g of 7-chloroisatoic anhydride (purity: 99%). The yield was 97% and the volume efficiency was 10.5 g/100 ml.

Comparative Example 1

According to the same manner as in Example 1 except that the volume of the flask was changed to 1 liter and water (87 g) was used in place of water and tetrahydrofuran, the reaction was conducted. The maximum value of the

volume of the reaction mixture was 350 ml.

According to the same manner as in Example 1, the reaction mixture was post-treated to obtain 4.12 g of 7-chloroisatoic anhydride (purity: 99%). The yield was 83% and the volume efficiency was 1.2 g/100 ml.

5 Example 3

10 Into a 200 ml flask equipped with a cooling apparatus (-20°C) were placed 53 g of water, 2.8 g of laurylpyridinium chloride and 18 g of 4-chloroanthranilic acid (purity: 98%). The mixture was cooled to 10°C with stirring and adjusted to pH 6 - 7 with addition of an aqueous sodium hydroxide. Then, the reaction was conducted while introducing phosgene into the vapor phase part of the reactor at a flow rate of 0.3 g/minute, cooling the reaction mixture so as to maintain the temperature at 5 - 15°C and adding an aqueous sodium hydroxide such that pH was maintained at 6 - 7.

When 23 g of phosgene was introduced, addition of the aqueous sodium hydroxide was stopped and introduction of phosgene was further continued until pH became 1.

15 After completion of the reaction, excess phosgene was exhausted by addition of methanol and crystals were filtered, washed with methanol and dried to give 18.5 g of 7-chloroisatoic anhydride (purity: 98%). The conversion of 4-chloroanthranilic acid was 98% and the yield was 91%.

The volume efficiency (yield of the objective product per maximum volume 100 ml the reaction mixture) was 10 g/100 ml.

20 Example 4

According to the same manner as in Example 3, except that 17 g of toluene and 2.9 g of laurylpyridinium chloride were used in place of 2.8 g of laurylpyridinium chloride and the flow rate of phosgene introduced was changed to 0.2 g/minute, 19.6 g of 7-chloroisatoic anhydride (purity: 99.7%) was obtained.

25 The conversion of 4-chloroanthranilic acid was 100%, the yield was 91% and the volume efficiency was 12 g/100 ml.

Comparative Example 2

30 According to the same manner as in Example 3, except that the flask was changed to 1 l flask, 88 g of water was added in place of water and laurylpyridinium chloride, an aqueous sodium carbonate was used in place of the aqueous sodium hydroxide and phosgene was changed to 5.2 g, 4.1 g of 7-chloroisatoic anhydride (purity: 99%) was obtained.

The conversion of 4-chloroanthranilic acid was 83%, the yield was 20% and the volume efficiency was 1.2 g/100 ml.

Comparative Example 3

35 The same manner as in Example 3 was conducted, except that phosgene was introduced without addition of laurylpyridinium chloride. The reaction mixture became a whipped cream mass with an increase in volume, thereby blocking the cooling apparatus. Therefore, the reaction was stopped when about 10 g of phosgene was introduced.

The conversion of 4-chloroanthranilic acid was 33%.

40 Comparative Example 4

45 According to the same manner as in Example 4, except that the flask was changed to 300 ml flask, laurylpyridinium chloride was not used, 103 g of water was added, and that amounts of toluene, phosgene and 4-chloroanthranilic acid were changed to 34 g, 40 g and 35 g, respectively, 35.6 g of 7-chloroisatoic anhydride (purity: 73.8%) was obtained. The yield was 67% and the volume efficiency was 9 g/100 ml.

Comparative Example 5

50 According to the same manner as in Example 3 except that laurylpyridinium chloride was replaced by 1.7 g of sodium laurylbenzene sulfonate and the amount of phosgene was changed to 30 g, 7-chloroisatoic anhydride was obtained.

The conversion of 4-chloroanthranilic acid was 69% and the yield was 64%.

55 Comparative Example 6

According to the same manner as in Example 3, except that laurylpyridinium chloride was replaced by 2.28 g of benzyl triethyl ammonium chloride and the amount of phosgene was changed to 30 g, 7-chloroisatoic anhydride was

obtained.

The conversion of 4-chloroanthranilic acid was 73%.

Example 5

To a 200 ml flask equipped with a condenser (-20°C), water (78.9 g), tetrahydrofuran (315.5 g) and 4,5-dimethoxyanthranilic acid (80.5 g, purity: 98%) were charged. After cooling to 20°C with stirring, an aqueous 25 % sodium hydroxide solution was added thereto so that the pH became 6 to 7. Then, the reaction was conducted while introducing phosgene in the vapor phase part of a reactor with a flow rate of 0.26 g/minute, cooling the reaction mixture so that the temperature was maintained at 15 to 25 °C, and adding an aqueous 25% sodium hydroxide solution so that the pH was maintained at 6 to 7.

After 47.5 g of phosgene has been introduced, the addition of the aqueous sodium hydroxide and phosgene was stopped and 18 % hydrochloric acid (11.7 g) was added so that the pH became 1.

According to the same manner as that in Example 3, a post treatment was carried out to obtain 79.6 g of 6,7-dimethoxyisatoic anhydride (purity: 88%). The yield was 83%.

Example 6

According to the same manner as in Example 5, except that 171.6 g of water and 171.6 g of toluene were used in place of 78.9 g of water and 315.5 g of tetrahydrofuran, and that 4-chloroanthranilic acid was used in place of 4,5-dimethoxyanthranilic acid, 80.9 g of 7-chloroisatoic anhydride (purity: 91 %) was obtained.

The yield was 93%.

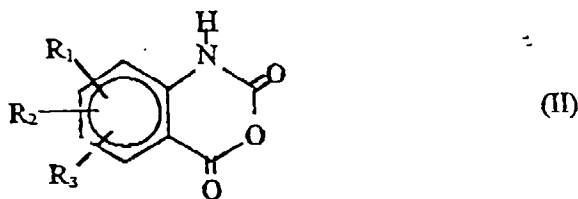
Example 7

According to the same manner as in Example 3, except that the flask was changed to 500 ml flask, 70 g of water, 280 g of toluene and 35 g of 4-chloroanthranilic acid were in place of 53 g of water and 2.8 g of laurylpyridinium chloride, and that the reaction temperature was maintained at 15 - 25 °C, 41.0 g of 7-chloroisatoic anhydride (purity: 94%) was obtained.

The yield was 98%.

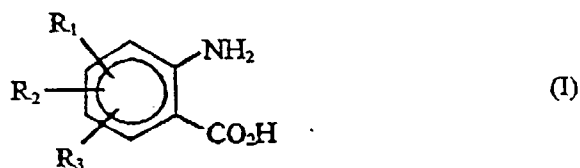
Claims

1. A process for producing isatoic anhydrides represented by the formula (II) :



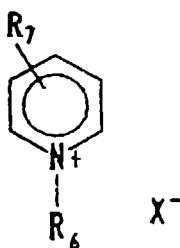
wherein R_1 and R_2 , which may be the same or different, each represent a halogen atom, a nitro group, a lower alkyl group which is optionally substituted with a halogen atom, an aralkyl group which is optionally substituted with a halogen atom, an alkoxy group which is optionally substituted with a halogen atom, an alkoxy-carbonyl group which is optionally substituted with a halogen atom, an acyloxy group or $XN R_4 R_5$ (X is a direct bond, a lower alkylene group or a carbonyl group provided that, when X is a direct bond or a lower alkylene group, R_4 and R_5 , which may be the same or different, each represent a lower alkyl group or N, R_4 and R_5 may form a five- or six-membered heterocycle which optionally contain another hetero atom and, when X is a carbonyl group, R_4 and R_5 , which may be the same or different, each represent a hydrogen atom or a lower alkyl group or N, R_4 and R_5 may form a five- or six-membered heterocycle which optionally contain another hetero atom and further, when containing another hetero atom, said hetero atom may be substituted.); and R_3 is a hydrogen atom, a halogen atom, a nitro group, a lower alkyl group which is optionally substituted with a halogen atom, an aralkyl group which is optionally substituted with a halogen atom, an alkoxy group which is optionally substituted with a halogen atom or an alkoxy-carbonyl group which is optionally substituted with a halogen atom, which comprises reacting phosgene

and an anthranilic acid represented by the formula (I) :



10 wherein R_1 , R_2 and R_3 are as defined above, or a salt thereof using a mixed solvent comprising water and an organic solvent which is miscible with water and inert to the reaction.

- 15
2. A process according to claim 1, wherein the mixed solvent is used in a 1- to 20-fold amount by weight relative to the anthranilic acid of formula (I) or salt thereof.
 3. A process according to claim 1 or 2, wherein the proportion of the organic solvent in the mixed solvent is from 1 to 99% by weight.
 - 20 4. A process according to claim 1, 2 or 3 wherein the organic solvent is a cyclic ether or glyme.
 5. A process according to claim 4, wherein the cyclic ether comprises tetrahydrofuran.
 - 25 6. A process for producing an isatoic anhydride of formula (II) as defined in claim 1 which comprises reacting phosgene with an anthranilic acid of formula (I) as defined in claim 1 or a salt thereof in the presence of an alkylpyridinium salt in an aqueous solvent.
 7. A process according to claim 6, in which the alkylpyridinium salt is a compound represented by the formula (III) :



(III)

40 wherein R_6 indicates an alkyl group having 8 - 20 carbon atoms, R_7 indicates a hydrogen atom or a lower alkyl group and X indicates an anion.

- 45
8. A process according to claim 6 or 7 wherein the amount of the alkylpyridinium salt is in a range of 0.005 - 0.5 fold by weight with respect to the amount of anthranilic acid compound of the formula (I) or salt thereof.
 9. A process for producing an isatoic anhydride of formula (II) as defined in claim 1 which comprises reacting phosgene with an anthranilic acid of formula (I) as defined in claim 1 or a salt thereof using a mixed solvent comprising water and an organic solvent which is substantially immiscible with water and is inert to the reaction, the amount of the organic solvent being from 1.5-20 fold by weight with respect to the amount of the anthranilic acid compound of the formula (I) or salt thereof.
 - 50
 10. A process according to claim 9 wherein the amount of the organic solvent is from 2.0 - 10 fold by weight by weight with respect to the amount of anthranilic acid compound of the formula (I) or salt thereof.
 - 55
 11. A process according to claim 14 wherein the organic solvent is selected from aromatic hydrocarbons, halogenated hydrocarbons and ethers.



European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 96 30 9490

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	FR 2 436 781 A (BERRI-BALZAC) * page 3 - page 4 *	1-11	C07D265/26
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Y	EP 0 621 262 A (HOECHST AG) * claims; examples 1-3 *	1-11	
A	DE 19 49 014 A (FARBENFABRIKEN BAYER AG) * claims; example 1 *	1-11	
D,A	JOURNAL OF ORGANIC CHEMISTRY, vol. 26, no. 2, 24 February 1961, EASTON US, pages 613-615, XP002026080 SHREEKRISHNA M. GADEKAR ET AL.: "Some halogenated 1,2,3-benzotriazin-4(3H)ones" * page 615, first column *	1-11	
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			C07D
Place of search THE HAGUE		Date of completion of the search 25 February 1997	Examiner Chouly, J
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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